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Amplified Halogen Bonding in a Small Space

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Supporting Information

ABSTRACT: Weak, intermolecular forces are difficult to observe in solution because the molecular encounters are random, short-lived, and overwhelmed by the solvent. In confined spaces such as capsules and the active sites of enzymes or receptors, the encounters are prolonged, prearranged, and isolated from the medium. We report here the application of encapsulation techniques to directly observe halogen bonding. The small volume of the capsule amplifies the concentrations of both donor and acceptor, while the shape of the space permits their proper alignment. The extended lifetime of the encapsulation complex allows the weak interaction to be observed and characterized by conventional NMR methods under conditions in which the interaction would be negligible in bulk solvent.

Halogen bonds are weak attractive forces between polarized halide donors and Lewis base acceptors (eq 1).[1,2] Typical donors are perfluorohalocarbons such as **1** and **2** or other halides with electron-withdrawing anchor groups (Figure 1); acceptors include nitrogen-containing heterocycles

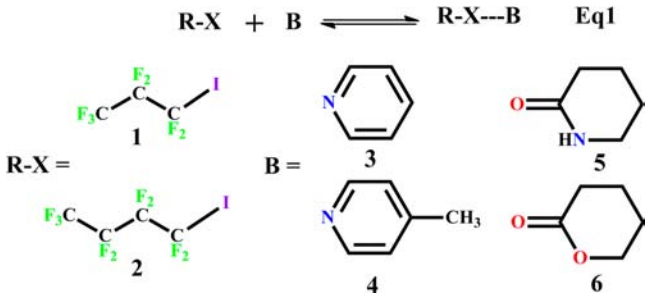

Figure 1. Halogen bonding (eq 1) and the donors (R-X) and acceptors (B) used.

such as pyridines **3** and **4** and oxygens of amides (**5**) and lactones (**6**). Even π bonds[3] and aromatic surfaces[4] can be modest acceptors. Like the related but much better-studied hydrogen bonds, the interaction is moderately directional with a preferred 180° arrangement of anchor (R), donor (X), and acceptor (B) atoms. Considerable research in halogen bonding has emerged in biology,[5] medicine,[6,7] soft materials,[8] and crystal engineering.[9,10] While the halogen bond is well-characterized in the solid phase[11] and on surfaces,[12] its very weakness and short lifetime render direct observation in solution[13] and supramolecular chemistry[14] difficult. In this Communication we show that reversible encapsulation offers a confined space that amplifies this interaction and allows its characterization through NMR spectroscopy, in solution and under ambient conditions.

Several self-assembled capsules have been used to amplify and stabilize complexes of hydrogen bonds,[15−17] but their attributes apply to halogen bonds as well: the size of the space—typically <1 nm^3—ensures molar concentrations of the occupants; the lifetime of the assemblies—milliseconds to hours—slows the exchange rates into and out of the capsule, and the temporary isolation prevents competing interactions with solvents from disrupting the complexes. The capsule **7.7** (Figure 2) offers the further advantage that the *shape* of its space and its chemical surface can align congruent guests in arrangements favorable to probe halogen bonding.[18]

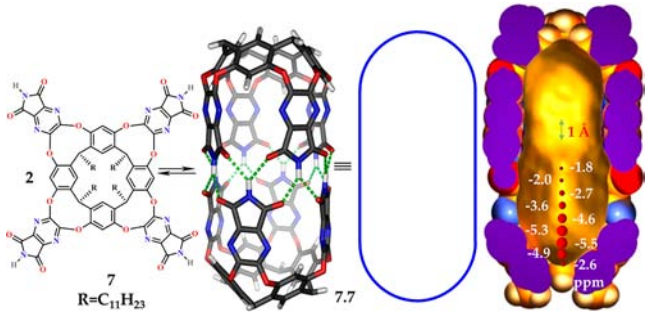

Figure 2. Chemical formula of the cavitand **7**, its computer-modeled dimeric capsule **7.7**, and the cartoon abbreviation used elsewhere in this work. Also shown is a cross-section of the capsule; the shape of the accessible space inside is highlighted in gold, and the calculated Nucleus Independent Chemical Shifts along its central axis are given in parts per million ($\Delta\delta$ ppm) scaled as red circles.

The cavitand **7** dimerizes in nonpolar media to form a capsule held together by eight bifurcated hydrogen bonds.[19] The eight aromatic panels of each cavitand provide a steric barrier between inside and outside and impart a stark magnetic anisotropy that shields nuclei inside during NMR experiments. The degree of shielding can be predicted through Nucleus

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Independent Chemical Shift (NICS) calculations,[20] and the values in parts per million (ppm) along the central axis of the capsule are reproduced[21] in Figure 2. They range from the largest effects at the ends of the capsule ($\Delta\delta$ = −5.5 ppm) to the smallest effects near the center ($\Delta\delta$ = −1.8 ppm). Nuclei closer to the capsule's aromatic walls show larger shifts.

Two molecules of the donor 1-iodo-perfluoropropane **1** are encapsulated by **7.7** in mesitylene-d_{12} solvent, and their orientations inside follow from the NICS values. Separate signals are seen in the NMR spectra for encapsulated species and their counterparts in solution. There is enough space in the capsule for the guest to tumble freely,[22] but comparison of the ^{19}F chemical shifts for free and encapsulated **1** (Figure 3) indicates that the I atoms reside near the tapered ends of the capsule as in Figure 3b.

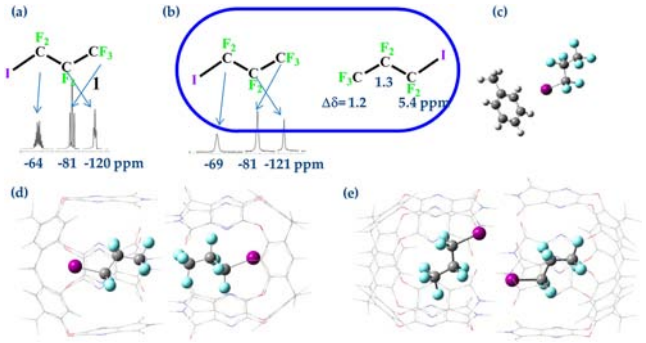

Figure 3. Observed ^{19}F NMR signals (400 MHz, mesitylene-d_{12}) for free **1** (a) and the changes in shifts ($\Delta\delta$ in ppm) of its encapsulation complex (b). The calculated[23,24] structure of **1** in contact with toluene (c) is from ref 4. Energy-minimized structure (d) is calculated[25] to be more stable than (e) by 2 kcal/mol (DFT/B3LYP)[26] and 9.3 kcal/mol (DFT/M062X).[27]

The only substantial upfield shift ($\Delta\delta$ = −5.4 ppm) seen for encapsulated **1** is at the -CF_2-I. This shift places these fluorines near the ends of the capsule where the magnetic shielding is greatest. There, the resorcinols present a "bowl" of four electron-rich aromatic panels, fixed in space and converging on the I atoms appropriately for halogen bonding. It is known that weak halogen bonds to **1** are formed with toluene in a 1:1 fashion as in Figure 3c and cause an upfield shift of the -CF_2-I signals of −2.5 ppm.[4] This interaction is also expected with the mesitylene solvent used in the present case. None of the ethereal oxygens of the capsule are properly oriented to contact the I atom. Both magnetic shielding anisotropy and halogen bonding contribute to the shifts observed (see Supporting Information (SI)).

Compound **1** forms only a weak halogen bond with γ-picoline **4** as shown by a 1.9 ppm upfield shift of the -CF_2-I signals in mesitylene solvent. The effect of fixing the halogen bonding partner in close proximity and proper alignment can be revealed in the confined space of **7.7**. A large change occurs in the ^{19}F spectrum on co-encapsulation of **4** with **1**. All signals shift upfield in the manner expected for halogen bonding (Figure 4): The fluorocarbon flips to make contact with the picoline N near the center of the capsule ($\Delta\delta$ = −12.2 ppm for the -CF_2-I); the CF_3 group is pushed into the resorcinarene ($\Delta\delta$ = −5.7 ppm) and pulls the central CF_2 closer to the ends of the capsule ($\Delta\delta$ = −3.3 ppm). Both the change in resonance at C_1 *and* the upfield shift of the terminal CF_3 are evidence of the attractive interaction between the I donor and N acceptor.

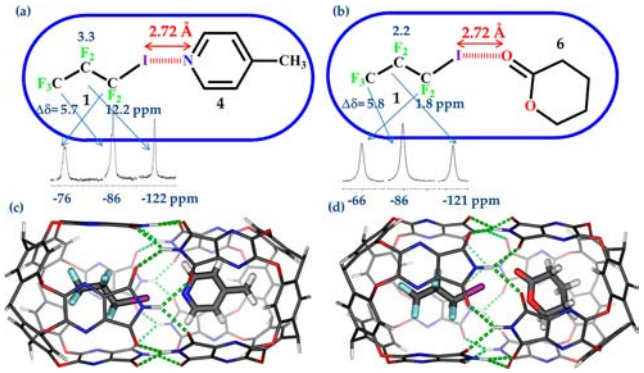

Figure 4. Co-encapsulation of acceptors γ-picoline **4** (a) and δ-lactone **6** (b) with donor **1**. The large shift ($\Delta\delta$ = −12.2 ppm) with **4** indicates strong N−I bonding. The smaller shift ($\Delta\delta$ = −1.8 ppm) with **6** indicates weaker O−I bonding. Calculated structures[23] are shown in (c) and (d).

The ^{1}H signal of the γ-picoline indicates that its CH_3 group is fixed at the end of the capsule ($\Delta\delta$ = −5.1 ppm).[28]

Oxygen acceptors that could co-encapsulate with **1** were also examined. While two molecules of the δ-lactam **5** were encapsulated as a stable homomeric complex, disproportionation of that assembly with complex in Figure 3b did not occur. Apparently, the hydrogen bonding between lactams in the homomeric capsule is energetically favored over halogen bonding in the heteromeric one. The corresponding δ-lactone **6** did coencapsulate with **1** and showed the shifts reported in Figure 4b. A weaker halogen bond is formed with the δ-lactone than γ-picoline, since smaller upfield shifts were observed for the nearby ^{19}F signals. The δ-lactone is a stronger halogen bond acceptor than the aromatic surface at the capsule's end since **1** flips to present the I atom to the lactone. Computed structures are shown in Figure 4c,d.

Other potential acceptors were tested for halogen bonding with **1** (Figure 5). Neither α-picoline **8** nor β-picoline **9** was observed to co-encapsulate with the perfluoroiodide. Like **4**, these picolines are guests,[28] but none of their social isomers[29] place the nitrogen atoms on the central axis of the capsule in the manner required for halogen bonding (see SI). However, a parallel experiment was performed using pyridine **3** and 1-iodo-

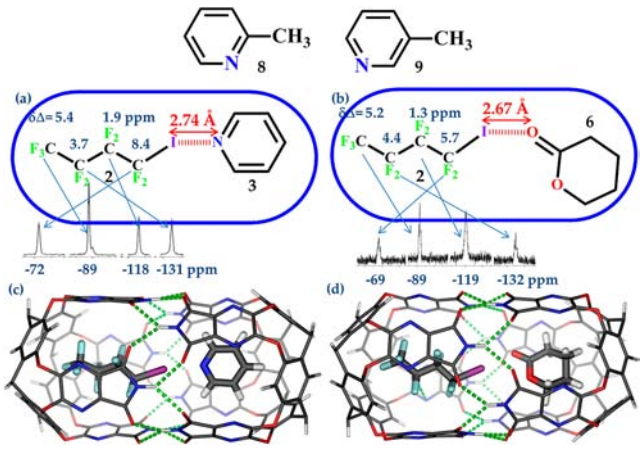

Figure 5. Co-encapsulation of acceptors pyridine **3** (a) and δ-lactone **6** (b) with donor **2**. The shifts (ppm) indicate both N−I and O−I halogen bonding. The bond distances shown are from the energy-minimized[23] structures (c) and (d).

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perfluorobutane **2**. This pair also fills the capsule's space properly since the longer donor complements the shorter acceptor. The chemical shifts shown in Figure 5a indicate halogen bonding occurs inside. Although this halogen bond is stronger than the same interaction in solution, it is weaker than that between **4** and **1**. The methyl of **4** fits the tapered end of the capsule where the CH/π interactions anchor it and ideally position the N for halogen bonding. The pyridine **3** lacks this preorganization; it is free to spin and tumble and has many ways to occupy the space, but only a few allow halogen bonding. A similar result was observed with the lactone **6** inside **7.7**. The longer **2** forms a stronger halogen bond with **6** presumably because donor and acceptor are forced to be closer to each other in the limited space (Figure 5b).

The energetic evaluation of intermolecular forces such as hydrogen bonding interactions is context dependent, whether in protein interiors,[30,31] grooves of nucleic acids,[32] or synthetic receptors.[33] Likewise, halogen bonding can be also observed in proteins,[34] membranes,[35] and synthetic receptors, but the weakness of the interaction often requires the presence of auxiliary attractive forces.[36] The isolation of the components in capsules permits direct observation; the weak attractions are amplified by the high concentrations and isolation from solvent, while the shape of the space in the capsule and its ability to align reagents within it give rise to selectivity that is not seen in solution. As a result, γ-picoline and pyridine can achieve positions for halogen bonding in the restricted space, but α- and β-picolines cannot.

■ ASSOCIATED CONTENT

Supporting Information

Details of the computations and ^{1}H NMR and ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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